Kidney International, Vol. 50 (1996), pp. 929–936

Use of vancomycin in high-flux hemodialysis: Experience with 130 courses of therapy

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Use of vancomycin in high-flux hemodialysis: Experience with 130 courses of therapy. Vancomycin is often administered to hemodialysis patients at long dosage intervals because its removal by hemodialysis is considered to be negligible. We and others, however, have demonstrated significant removal of vancomycin by high-flux hemodialysis. This report describes our experience with 89 courses of vancomycin using a revised regimen with a loading dose followed by 500 mg doses after each dialysis treatment, and compares results with 41 courses using single weekly dosing. All patients were dialyzed with high-flux membranes using volumetric ultrafiltration and bicarbonate dialysate. Serum vancomycin levels were obtained two hours after completion of infusion (peak) and immediately prior to dialysis (trough) and were measured by Abbot TD_X fluorescence polarization immunoassay. Duration of multiple-dose therapy was 11 ± 8 days, with mean total dose 3.6 ± 1.8 g. Initial doses of 20 mg/kg rapidly and reliably established therapeutic pre-dialysis serum levels (10 to 25 μg/ml). In patients treated with multiple dosing, 431 pre-dialysis levels were obtained. The mean level was 15.9 ± 5.7 μg/ml; 55 levels (13%) were less than 10 μg/ml and 22 (5%) were above 25 μg/ml. In patients treated once weekly, 77% of levels were below 10 μg/ml by five days after administration, and 84% at one week. No patient developed demonstrable ototoxicity. Twenty-five patients were treated for ≥ two weeks, five for ≥ four weeks, and two for > five weeks, with no evidence of toxic accumulation. Mean peak level was 20.1 ± 4.6 μg/ml, with a mean difference from preceding pre-dialysis level of 7.2 ± 2.2 μg/ml. We conclude that in high-flux hemodialysis, a 20 mg/kg loading dose of vancomycin followed by 500 mg doses after each dialysis treatment achieves predictable, adequate and safe therapeutic levels, does not lead to unacceptably high peaks, and does not accumulate during long treatment courses. By contrast, once-weekly vancomycin dosing resulted in subtherapeutic serum levels after five to seven days, and should be abandoned in the high-flux setting.

Vancomycin is frequently administered to patients on hemodialysis because of its activity against gram-positive organisms–probably the most common infecting agents in chronic dialysis patients [1–7]. It is excreted almost entirely by glomerular filtration, and the elimination half-life, which is approximately nine hours with normal renal function [8, 9], in end-stage renal disease is markedly prolonged to between 54 and 180 hours [9–13]. Since the clearance of vancomycin by hemodialysis has been considered negligible, this prolonged half-life should allow the use of administration schedules with quite long dosage intervals, and single weekly doses of one gram have been used for more than a decade.

Received for publication February 12, 1996
and in revised form April 4, 1996
Accepted for publication April 8, 1996

Recent investigations in our and other centers, however, have indicated that use of new high-permeability dialysis membranes results in significant removal of vancomycin [12–25].

Our own experience [12, 18, 20] has indicated a marked (33.5 ± 2.4%) reduction in serum vancomycin levels during dialysis using large surface area high-flux dialyzers, leading to persistently low (< 10 μg/ml) serum levels during the week between 1000 mg doses, and we have frequently observed susceptible gram-positive infections that failed to respond readily to vancomycin therapy. Nevertheless, a role for vancomycin in the empiric treatment of infections in dialysis patients seems indisputable: in the last 125 gram-positive bacteremic infections in our center, 95% showed *in vitro* susceptibility to vancomycin. No other bactericidal antibiotic was effective on more than 53% of isolates (Fig. 1) [6].

We therefore instituted a revised regimen for vancomycin therapy [18] using a loading dose followed by 500 mg doses after each dialysis treatment. This report describes the pharmacokinetic experience with 89 courses of therapy using this revised dosing strategy, and compares results obtained with 41 courses using single weekly dosing.

Methods

Patients

One hundred thirty courses of vancomycin (cases) were administered to 69 men and 1 woman (patients) between January 1990, and September 1995. All were receiving chronic maintenance hemodialysis; 32 (46%) were diabetic. The mean patient age was 64.0 ± 11.6 years and mean weight was 70.3 ± 14.3 kg.

Hemodialysis

All patients were dialyzed with high flux dialyzers, as shown in Table 1, at blood flow rates of 400 to 600 ml/min, using volumetric ultrafiltration dialysis systems (Monitral, Fresenius) and bicarbonate dialysate. Dialysis frequency was twice weekly in 29 cases (interdialytic interval 3.3 ± 0.4 days) and three times weekly in 101 cases (interdialytic interval 2.3 ± 0.2 days), with a session duration of 3.3 ± 0.4 hr. Urea reduction ratio (URR), measured during 116 courses of therapy, was 63.6 ± 8.3%.

Vancomycin administration

In all cases, vancomycin was administered in the hemodialysis unit for a therapeutic indication (Table 2); in some cases, more than one indication was present. The drug was diluted in 100 to 250 ml 0.45% NaCl and administered as an intravenous infusion over 30 to 60 minutes, following the completion of hemodialysis.

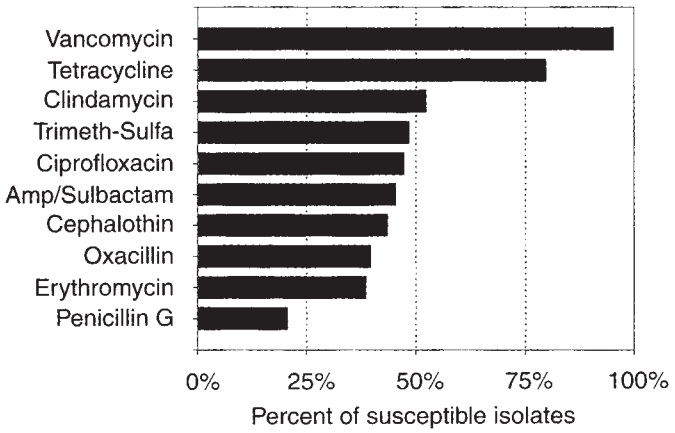

Fig. 1. *Antibiotic susceptibilities of organisms isolated from 125 consecutive cases of gram-positive bacteremia at the Brooklyn VAMC hemodialysis unit.*

Table 1. Dialyzers used

Dialyzer (manufacturer)	Type[a]	Membrane	Surface area	K_OA[b]	*N*
F60 (Fresenius)	HF	Polysulfone	1.2 m^2	532	13
F80 (Fresenius)	HF	Polysulfone	1.8 m^2	572	94
B1 2.1U (Toray)	HF	Polymethylmethacrylate	2.1 m^2	651	4
Biospal (Hospal)	PP	Sulfonated polyacrylonitrile	1.0 m^2	243	3
Filtral 12 (Hospal)	HF	Sulfonated polyacrylonitrile	1.2 m^2	323	2
Filtral 16 (Hospal)	HF	Sulfonated polyacrylonitrile	1.7 m^2	436	17
Total[c]					133

[a] HF = hollow fiber, PP = parallel plate
[b] K_OA calculated from direct quantification of dialysate urea
[c] In 3 cases more than one dialyzer was used during a course of therapy

In 41 cases, patients received a single dose of vancomycin, while in 89 cases patients received a loading dose followed by 500 mg after every successive dialysis until therapy was complete. During the first two years of the investigation the initial dose in both groups was 1000 mg, and in 1993 the initial dose was changed to 20 mg/kg.

Vancomycin serum levels

Peak serum vancomycin levels were drawn two hours after the end of the infusion to ensure completion of the distribution phase [26–28]. "Trough" levels were drawn prior to the initiation of successive hemodialysis treatments. In patients treated with a single dose, levels were measured for at least one week. In patients receiving multiple doses, levels were measured until the dialysis treatment following the last dose. Since not all patients were dialyzed with the same schedule, numbers of data points differed at different times following the initial dose. All levels were assayed using the TD_X fluorescence polarization immunoassay (Abbot Diagnostics, Irving, TX, USA) [29].

Table 2. Indications for vancomycin therapy

	Multiple dose	Single dose
Fever	29	18
Bacteremia		
Enterococcal	3	0
Pneumococcal	1	0
Staphylococcal	14	2
Soft-tissue infections	9	5
Vascular access infections	13	1
Percutaneous catheter infection	9	3
Respiratory infection	4	3
Urinary tract infections	2	3
Endocarditis prophylaxis (dental procedures)	0	3
Endocarditis	3	0
Osteomyelitis	1	0

Table 3. Initial vancomycin dose

	Initial dose *mg*	Initial dose *mg/kg*	*N*[a]
Single dosing			
20 mg/kg	1296 ± 250	19.6 ± 1.7	28
1000 mg	1000	14.9 ± 3.3	27
Overall	1198 ± 247	17.3 ± 3.7	40
Multiple post-hemodialysis dosing			
20 mg/kg	1367 ± 262	19.9 ± 1.7	57
1000 mg	1000	15.4 ± 3.2	37
Overall	1203 ± 326	17.3 ± 4.1	89

[a] Some overlap is present, since in some patients a dose of 20 mg/kg was actually 1000 mg

Statistics

Non-parametric (Mann-Whitney *U*-test) or parametric (*t*-test) analysis of differences between group means were carried out as appropriate. Comparison of frequency distributions was carried out using the chi-square test with Yates correction for continuity. Unless otherwise specified, data are reported as mean ± SD.

Results

Vancomycin was administered using the multiple post-dialysis dosing regimen to 89 patients, who received from 2 to 24 doses each (median 5), for a mean total dose of 3.6 ± 1.8 g (range 1.5 to 13.2 g). The mean duration of therapy was 11 ± 8 days (range 3 to 54 days). Single weekly doses were administered to 41 patients. Initial doses in both groups were similar (Table 3). There were no differences between patients in the single-dose and multiple-dose groups with respect to age, weight, URR, or percentage of diabetics. The patients treated with a single dose had a longer interdialytic interval (2.7 ± 0.5 vs. 2.5 ± 0.4 days, $P < 0.02$) and fewer weekly hours (8.8 ± 1.9 vs. 9.7 ± 1.7 hr, $P < 0.01$) of dialysis than the patients who received multiple dosing.

The initial vancomycin dose in mg/kg body wt was strongly correlated with the serum level at 48 hours (Fig. 2). In the group of patients given multiple doses, a loading dose of 20 mg/kg resulted in more rapid achievement of levels greater than 10 μg/ml during the first week than did a loading dose of 1000 mg. In the 20 mg/kg group, 6 of 92 levels (7%) during the first five days of therapy were below 10 μg/ml, while in the 1000 mg group, 17 of 56 (30%) were less than 10 μg/ml ($P < 0.001$). By seven days after

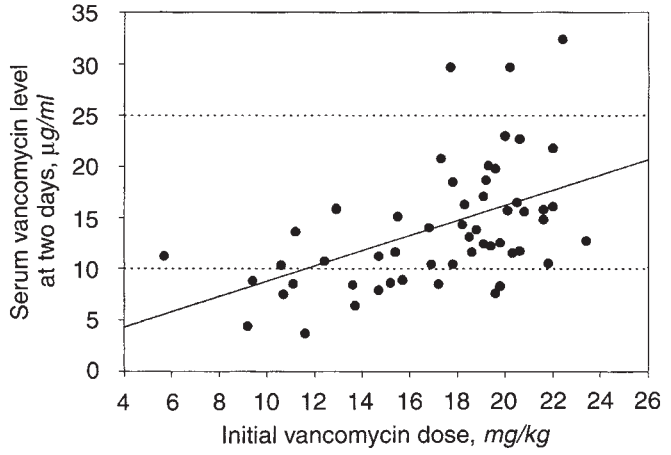

Fig. 2. *Pre-dialysis serum vancomycin levels 48 hours after administration, as a function of initial dose,* N = *56.* The equation of the regression line is y = 0.75x + 1.33; $r = 0.49$ ($P < 0.001$).

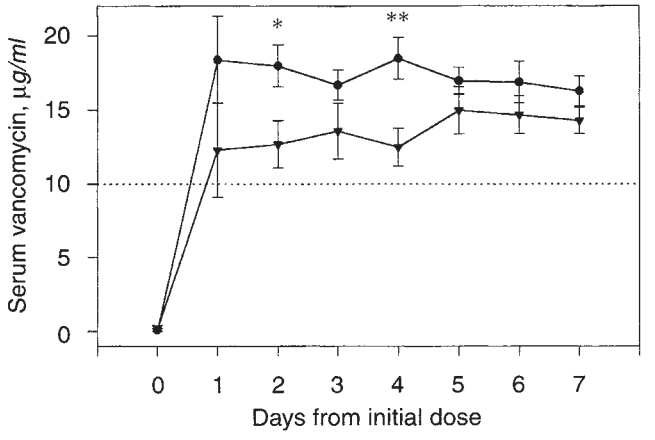

Fig. 3. *Mean pre-hemodialysis serum vancomycin level ± SEM for patients treated with multiple 500 mg post-dialysis doses and either a 20 mg/kg (●,* N = *50) or a 1000 mg (▼,* N = *36) loading dose.* $*P < 0.02$; $**P < 0.01$ for differences between mean values. Dotted line indicates the lower limit of the therapeutic range.

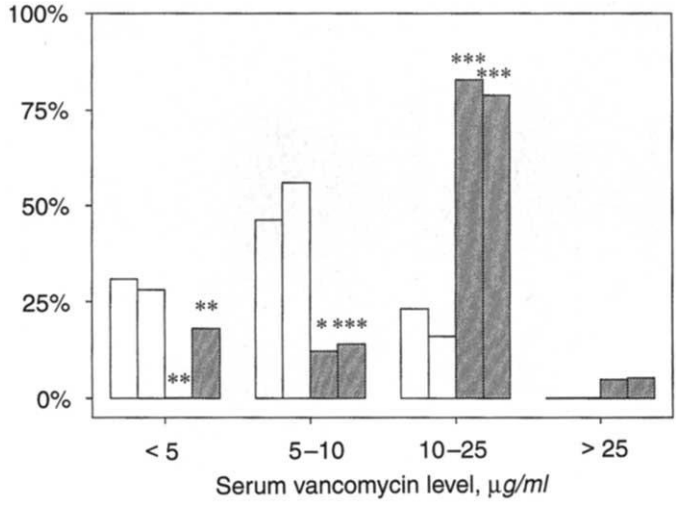

Fig. 4. *Distribution of vancomycin levels at five days (first bar) and seven days (second bar) after initial dose.* Symbols are: (□) patients given single weekly doses; and (▨) those given multiple post-dialysis doses. For single doses, $N = 13$ at five days, $N = 25$ at seven days. For multiple doses, $N = 41$ at five days, $N = 57$ at seven days. $*P < 0.025$, $**P < 0.005$, $***P < 0.001$ for difference from single dose therapy.

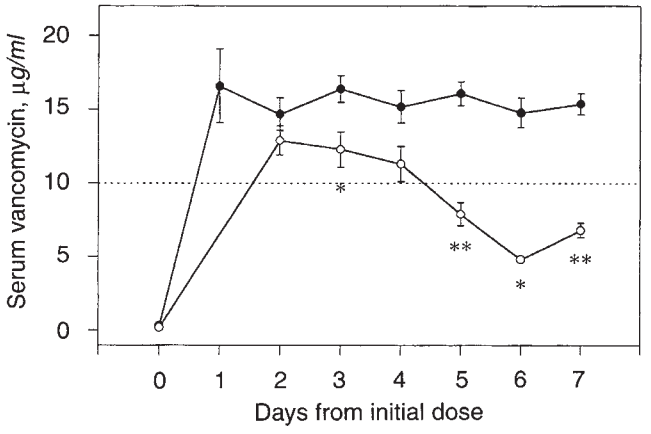

Fig. 5. *Mean pre-hemodialysis serum vancomycin level ± SEM through one week of therapy in patients treated with a single weekly dose (○,* N = *41) or with a loading dose followed by multiple 500 mg post-hemodialysis doses (●,* N = *89).* $*P < 0.02$; $**P < 0.001$ for differences between mean values. Dotted line indicates the lower limit of the therapeutic range.

the loading dose, there was no longer a difference in the distribution of levels in patients given initial doses of 1000 mg or 20 mg/kg. Figure 3 shows the mean pre-dialysis serum levels for patients given multiple doses with a 20 mg/kg loading dose and with a 1000 mg loading dose. In patients receiving a single weekly dose, the mean levels were somewhat higher throughout the week in the group receiving 20 mg/kg, but the differences were not statistically significant.

At five days and one week after the initial dose, levels were distributed as shown in Figure 4. At five days after administration, single-dose therapy resulted in serum levels which were below 10 μg/ml in 77% of cases and below 5 μg/ml in 30%. At one week, levels were less than 10 μg/ml in 84% and less than 5 μg/ml in 28%. By contrast, in patients treated with multiple doses only 12% were below 10 μg/ml at five days and 16% at one week, and only one of 98 serum levels obtained at five days and one week was less than 5 μg/ml. A comparison of levels through the first week of therapy in patients given single and multiple doses is shown in Figure 5.

Overall, in patients treated with multiple doses, 60.6% of 431 pre-hemodialysis trough levels fell between 10 and 20 μg/ml, and 82.8% were between 10 and 25 μg/ml, while only 12.1% were below 10 μg/ml. Twenty-five patients were treated for ≥ two weeks, 5 for ≥ four weeks, and 2 for > five weeks, with no evidence of toxic accumulation of vancomycin. Only 22 of 431 trough levels (5.1%) exceeded 25 μg/ml. The histogram in Figure 6 shows the overall distribution of serum levels in patients treated with multiple dosing. Figure 7 shows the mean serum vancomycin levels ± SD through 21 days for all patients treated with multiple dosing. In the five patients treated with multiple doses for four

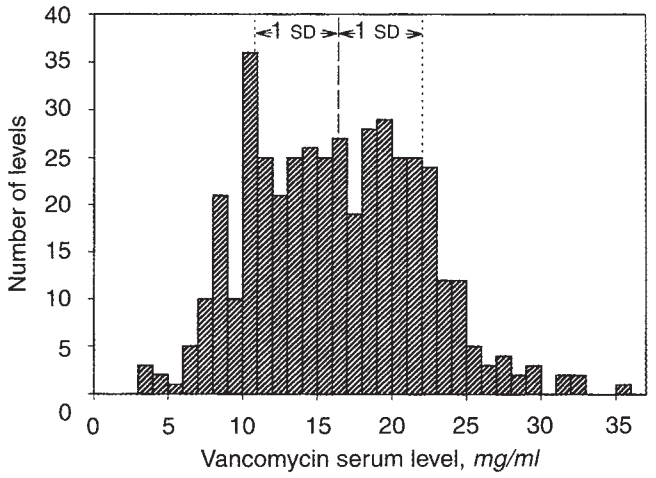

Fig. 6. *Histogram showing distribution of pre-hemodialysis serum vancomycin levels in patients treated with multiple 500 mg post-dialysis doses.* Lines indicate mean ± SD.

weeks or more, mean serum level during the period from days 22 to 45 was 18.6 ± 3.7 μg/ml (range 10.4 to 27.7, $N = 29$).

Serial peak levels ($N = 18$) were measured in six patients two hours after 500 mg doses. The overall mean peak level was 20.1 ± 4.6 μg/ml (range 12.2 to 29.8), and mean difference from preceding pre-dialysis level was 7.2 ± 2.2 μg/ml (range 3.8 to 11.7). Figure 8 shows mean serial changes in serum vancomycin level through one hemodialysis cycle.

Infection resolved in almost all patients. In the multiply dosed group, two patients required surgical excision of an infected PTFE graft, one required removal of a percutaneous catheter, and one had relapse of staphylococcal endocarditis.

"Red man syndrome" occurred five times, and resulted in discontinuation of therapy in one case. There were no other symptoms attributable to vancomycin. Audiometry performed in two patients with maximum trough levels of 23.0 and 23.7 μg/ml revealed no hearing loss.

Discussion

Evaluation of vancomycin dosing regimens is rendered problematic by the scarcity of data relating serum levels to therapeutic efficacy [28, 30–35]. In fact, the original recommended ranges for peak (30 to 40 μg/ml) and trough (5 to 10 μg/ml) levels were based on an estimation of serum levels which could be expected with the entirely empirical "standard" vancomycin regimen of 2 g/day in a 70 kg man with normal renal function, rather than on data regarding efficacy or toxicity [28, 36]. Much is known, however, about the pharmacokinetics and pharmacodynamics of vancomycin, and some conclusions may be drawn regarding desirable levels in dialysis patients.

The target of therapy with vancomycin in the majority of cases is a presumed or definite infection with staphylococci. Data from several sources indicate that the bactericidal activity of vancomycin against these organisms is not concentration dependent once the minimal inhibitory concentration (MIC) has been exceeded, and that high peak levels are not therefore necessary for therapeutic efficacy [37–39]. Monitoring of peak levels thus serves primarily to prevent toxicity, especially ototoxicity [40]. Ototoxicity from vancomycin alone appears to be extremely rare [30–32, 41], however, so much so that the necessity for monitoring peak levels at all has been questioned [30–32, 40, 42–44]. In any case, maintaining peak levels less than 40 to 50 μg/ml (measured 1 to 2 hr after the completion of infusion) should almost certainly prevent the occurrence of any irreversible hearing loss.

Given the low likelihood of vancomycin toxicity, especially in the dialysis patient who is not susceptible to nephrotoxicity, the focus of pharmacokinetic monitoring should be on assuring that vancomycin serum levels do not drop below a therapeutically effective threshold. The MIC for most staphylococcal species is between 0.1 and 5.0 μg/ml [45, 46], although there have been increasingly frequent observations of higher MICs, especially in coagulase-negative species [47, 48]. MICs and minimal bactericidal concentrations (MBCs) may also be much higher in the presence of catheters or other foreign material [49–52], including polytetrafluoroethylene [53], the material used for almost all prosthetic arteriovenous fistulas in dialysis patients. Effectiveness of vancomycin in serum is lessened by its 40 to 60% protein binding [54], and tissue drug levels may be substantially lower than simultaneous serum levels: 52% in heart valves, 30% in subcutaneous tissue, 27% in muscle [55], 17% in pulmonary alveolar fluid [56], and 15% in bone [57]. A trough serum level of 5 μg/ml may therefore frequently be inadequate to eradicate staphylococci from a tissue site, especially in the presence of a catheter or prosthetic dialysis access.

A further consideration in dialysis patients is the cross-reactivity in the commonly used TD_X fluorescence polarization immunoassay of an inactive vancomycin metabolite, CDP-1, which accumulates over time and may lead to an overestimation of serum vancomycin levels by as much as 40% [42, 58–61]. Thus, when measured by this assay, levels that appear to be in the therapeutic range may in fact fall short.

The need for trough levels higher than the originally proposed 5 to 10 μg/ml has been reflected in recommendations made by a number of authors based on theoretical or clinical considerations (Table 4). There have also been two recent reports in which outcome in infections treated with vancomycin was found to be related to trough levels [66, 67]. More rapid resolution of fever and leukocytosis in patients with gram-positive bacteremia was associated with trough vancomycin levels greater than 10 μg/ml in one [66], and in the second mean trough vancomycin levels of less than 12 μg/ml predicted relapse of gram-positive peritonitis in patients on peritoneal dialysis [67]. Finally, because of the extremely prolonged half-life of vancomycin in end-stage renal disease, serum levels in dialyzed patients approximate a continuous infusion; several authors have recommended a steady-state level for continuous therapy of 15 μg/ml [68, 69].

Considering all of the above data, we believe trough levels below 10 μg/ml to be probably therapeutically inadequate in dialysis patients, that the desirable range for trough (pre-dialysis) serum vancomycin levels should be 10 to 20 μg/ml, and that peak levels less than 40 μg/ml are acceptably safe.

Examining the results of 500 mg post-dialysis doses of vancomycin in this context, we found that single weekly doses produced serum levels which were likely to be subtherapeutic by five days following administration of the drug. Table 4 shows that in patients given single weekly doses, 77% of serum vancomycin levels were less than 10 μg/ml by five days after dosing and 31% were below 5 μg/ml. The use of a 20 mg/kg dose rather than the

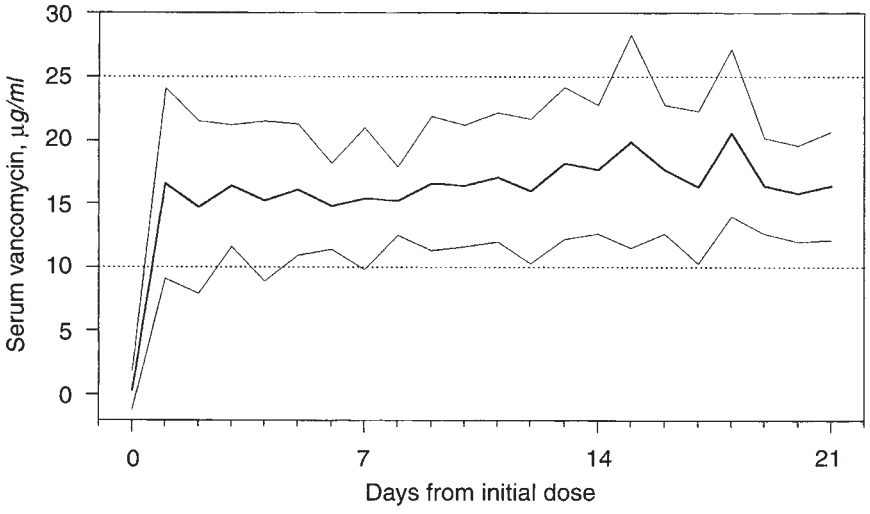

Fig. 7. *Mean pre-hemodialysis serum vancomycin level ± SD through three weeks of therapy for all patients treated with multiple 500 mg post-dialysis doses.*

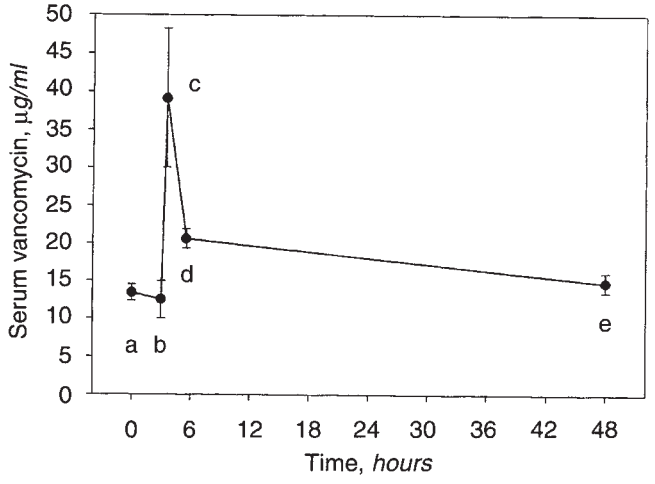

Fig. 8. *Mean serum vancomycin level ± SEM through 1 hemodialysis cycle in 14 cases.* **a**, pre-hemodialysis; **b**, post-hemodialysis; **c**, 15 minutes after completion of vancomycin infusion; **d**, two hours after completion of infusion; **e**, prior to next hemodialysis. $N = 14$.

Table 4. Recommended trough serum vancomycin levels

Authors [Ref]	Year	Level μg/ml
Normal renal function		
Geraci [62]	1958	8–10
Schaad et al [63]	1981	12
Healy et al [64]	1987	10–15
Glew [65]	1992	10–15
Ackerman & Vannier [42]	1992	10–12
Dialysis patients		
Ackerman & Vannier [42]	1992	12–15
Keller et al [24]	1994	10–20

"standard" 1000 mg weekly dose did not improve results: at one week 13 of 16 levels (81%) were below 10 μg/ml and 4 of 16 (25%) were less than 5 μg/ml. In contrast, in patients given 500 mg after each dialysis, only 12% of levels were below 10 μg/ml at five days and 18% at seven days, and in only one instance out of 98 levels measured at five and seven days was the serum level below 5 μg/ml. An initial dose of 18 to 22 mg/kg more rapidly and more reliably led to levels in the therapeutic range than lower loading doses. Overall, 47 of 433 levels (11%) measured in multiply-dosed patients were less than 10 μg/ml and only 5 of 433 (1%) were below 5 μg/ml (Fig. 2). Adequate therapeutic levels were thus consistently achieved by this regimen.

Apart from a few episodes of the anaphylactoid "red man" reaction, there was no clinically overt toxicity attributable to vancomycin. Eighteen peak levels were measured two hours after completion of the infusion, and the range was 12.2 to 29.8 μg/ml, with a mean value of 20.1 ± 4.6 μg/ml. Mean increase from the preceding trough value was 7.2 ± 2.2 μg/ml. Saunders measured 165 paired trough-peak values in patients treated with vancomycin, and found a mean increase of 16.6 μg/ml [40], but the patients were not on dialysis, and doses ranged from 500 to 1500 mg. Nonetheless, Saunders' data probably define the upper limit value for rise in level after a dose; it is unlikely that patients on high-flux dialysis would ever achieve this degree of increase, since a dialysis is performed between the "trough" level and the following peak, with significant removal of vancomycin. Our trough levels were not true troughs, in the sense of the level immediately preceding a dose, but they were presumably the lowest serum levels during a long (24 to 96 hr) interdialytic period, and thus in practical terms the lowest level attained during more than 90% of the interval between doses. Using pre-dialysis levels as troughs avoids the uncertainty introduced by the dialytic removal of vancomycin from the intravascular space and subsequent rebound of unpredictable timing and degree as the drug is redistributed from the peripheral compartment [13, 16, 22]. Our peak levels should represent true peaks, since by three hours after the completion of dialysis when they were drawn, most of the rebound effect is complete.

There were 22 trough levels (5%) in our patients that were greater than 25 μg/ml (range 25.2 to 35.0 μg/ml, median 27.8 μg/ml), which might raise some concern about potential toxic levels after the following dose. Even if a rise in level similar to that described by Saunders in undialyzed patients were to be obtained,

however, the following peaks would have been 42 to 52 μg/ml, for the most part within recommended limits for peak levels. Moreover, as discussed above, so great a rise would be unlikely.

We are unable to comment on differences in outcome between the multiply dosed and single dosed groups, since no attempt was made to randomize patients to the various therapeutic strategies. Given the need for surgical intervention in three of the patients treated with multiple doses, the single dose group might have seemed to do better. However, this is at least in part because patients who received single dose therapy were selected to have less severe disease. We did not feel it ethically defensible to treat a severe, deep staphylococcal infection with single weekly dosing. In fact, many of the patients who received weekly dosing were treated for superficial soft-tissue infections or endocarditis prophylaxis for dental procedures (Table 2).

Despite limitations on vancomycin use necessitated by the increasing emergence of resistant strains of gram-positive bacteria, especially enterococci [70, 71], this antibiotic remains extremely important in the therapy of bacterial infections in patients on hemodialysis. The large majority of those infections are caused by gram-positive organisms [1–7], and in many institutions, including our own, the prevalence of methicillin-resistance is high among both coagulase-positive and negative *Staphylococci* (Fig. 1), making vancomycin a compelling choice for initial therapy of apparent systemic infections. Further, the therapy of serious gram-positive infections in dialysis patients is frequently complicated by extreme difficulty in maintaining intravenous access. In such situations, the ability to administer vancomycin every 48 to 72 hours via the hemodialysis line is a very great advantage, and its choice is again favored, even though it may be less rapidly bactericidal for staphylococci than are beta-lactam agents [72–74].

Given the serious nature of the frequent systemic staphylococcal infections in dialysis patients, and the extreme rarity and dubious dose-dependency of vancomycin toxicity [35], it is crucial to maintain effective serum levels throughout therapy, while limiting peak concentrations is less important. In patients treated with high-flux hemodialysis, the vancomycin regimen presented here—a loading dose of 20 mg/kg followed by 500 mg after each hemodialysis treatment—rapidly achieved pre-dialysis trough serum levels of between 10 and 15 μg/ml, and resulted in plateau steady-state trough levels between 15 and 25 μg/ml after two to three weeks. Peak levels following the 500 mg doses were 5 to 10 μg/ml higher than pre-dialysis trough levels and rarely exceeded 35 μg/ml. Once-weekly dosing with 1000 mg or with 20 mg/kg led to levels which are probably subtherapeutic (< 10 μg/ml) in over 75% of cases by five days after administration, and in 84% of cases at one week. Even using the more conservative threshold value of 5 μg/ml, 30% of serum levels were subtherapeutic five days after a single vancomycin dose.

Most of the previously published investigations of vancomycin in high-flux dialysis have been short-term studies of pharmacokinetics in small numbers of patients; only two have studied multiple dosing during actual therapeutic use for periods longer than one week [18, 24], and in both of those studies only a small number of patients was treated. In a pharmacokinetic study in of eight uninfected dialysis patients, Pollard et al [13] concluded that single weekly vancomycin dosing with 20 mg/kg was sufficient in high-flux dialysis. In 16 of our patients who received one weekly dose of 20 mg/kg, mean pre-dialysis serum level at one week was 7.1 ± 2.8 μg/ml, significantly lower than that found by Pollard et al (9.7 ± 1.0, $P < 0.02$). This difference might be accounted for by the earlier study's selection of patients with no residual renal function, and perhaps by the significantly lower dose of dialysis administered in that study. In any case, Pollard et al based their dosing recommendations on a target trough vancomycin level of 5 to 10 μg/ml, which we feel, for reasons discussed above, to be inadequate. In fact, five of their eight patients had serum vancomycin levels lower than 10 μg/ml after one week. In another retrospective study of patients treated with both conventional and high-flux dialysis using multiple dosing, Keller and associates reached a similar conclusion to ours; that is, that administration of 500 mg doses after each dialysis is necessary to maintain therapeutically effective levels [15, 22, 24].

The dose of dialysis administered to our patients resulted in a urea reduction ratio of 64 ± 8%. There is reason to believe that morbidity and mortality may be reduced by more intensive dialysis than this [75–77], which may become more and more common. A higher dialysis dose might magnify the difference between single- and multiple-dose vancomycin therapy by increasing dialytic removal of vancomycin, leading to even longer duration of subtherapeutic levels in patients treated with single weekly doses.

A final consideration in comparing multiple and single weekly dose vancomycin therapy is the difference in cost between the two regimens; specifically, the potential for major increases in expense with the use of more frequent dosing. Vancomycin has been available as a generic preparation for some time, and is not currently among the most expensive antibiotics (the cost to our hospital pharmacy is $5.95/1000 mg) and the infrequent dosing used in dialysis patients makes the cost of therapy almost inconsequential. The mean cost of the first (that is, most expensive) week of multiple dose therapy in our patients (mean dose 2158 mg) was $12.84, and the mean weekly cost over the first four weeks of multiple dose therapy (mean dose 1387 mg) was $8.25. The mean cost of the first week of single weekly dose therapy (mean dose 1198 mg) was $7.13. The small difference in cost between single weekly and multiple dose therapy is thus not a major factor in choosing between these regimens.

We conclude that in high-flux hemodialysis, a 20 mg/kg loading dose of vancomycin followed by 500 mg doses after each dialysis treatment achieves predictable, adequate and safe therapeutic levels, does not lead to unacceptably high peaks, and does not accumulate during long treatment courses. By contrast, once-weekly vancomycin dosing results in subtherapeutic serum levels after five to seven days, and should be abandoned in the high-flux setting for the treatment of all but the most superficial bacterial infections.

Acknowledgments

This material has been partially published in abstract form (*J Am Soc Nephrol* 6:519; 1995) and was presented at the 28th Annual Meeting of the American Society of Nephrology (San Diego, 1995). The authors are grateful to Drs. Philip Goldwasser, John M. Quale, David Landman, Geoffrey M. Berlyne, and Edmund Bourke for review of the manuscript and helpful suggestions, to Carmine Caruso for technical assistance, and to the Dialysis Nursing Staff of the Brooklyn VA Medical Center for unflagging cooperation and assistance.

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